

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 2, 4-9, 14, 17, 20, 37-40, 47, 50-54, 57, 59, 61, 64-69, 71-76, 78-82 are pending in the application, with 1, 2, and 47 being the independent claims. Claims 3, 10-13, 15-16, 18-19, 21-36, 41-46, 48-49, 55, 56, 58, 60, 62-63, 70, and 77 have been cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1, 2, 4, 5, 14, 17, 20, 47, 50, 57, 59, 61, 71, 78-80 have been amended. It is believed these changes introduce no new matter, and their entry is respectfully requested.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 5 was rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for reciting "mutants and fragments thereof." (Office Action, p. 3.)

Applicants respectfully traverse the rejection.

Applicants have amended claim 5 to omit the phrase "mutants and fragments thereof." Accordingly, the rejection has been rendered moot. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph - written description

Claims 1-9, 11, 12, 14, 15, 17, 18, 20, 37-40, 43-48, and 50-82 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventors had possession at the time the application was filed. Office Action, p. 4. The Office Action expressed the concern that the claims encompass any polymerase modified at the recited positions, and the concern that "the skilled artisan may not be able to determine those amino acid residues which correspond to Arg722 or Lys726 for many of the modified polymerases of the genus . . . [or] modify these amino acids such that the modification results in the desired activity." Office Action, p. 6. Applicants respectfully traverse.

As recently reiterated by the Federal Circuit, the crux of the question concerning whether a claimed invention is adequately described is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention in the specification as filed. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1320 (Fed. Cir. 2003) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991)); *see also* M.P.E.P. § 2163.02. The Federal Circuit in *Eli Lilly* set forth several tests for whether a claimed genus is adequately described, including the "representative number of species" test and the "common structural features" test. *Regents of the Univ. of Calif. v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). However, the court also stated that "[w]e will not speculate in what *other ways* a broad genus of genetic material may be properly described." *Id.* (emphasis added).

In fact, subsequent to *Eli Lilly*, the Federal Circuit instructed that *functional* descriptions of biological material can satisfy the written description requirement if a structure/function correlation is known in the art. *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003).¹ The Federal Circuit has also reasoned, in reference to the recitation of known biological materials, that a description of a genus by words alone is sufficient if one of ordinary skill could recognize the members of the genus. *Amgen* at 1332. In addition, the Federal Circuit and the PTO have acknowledged that a specification may adequately describe a genus even though it fails to describe a single species falling within the genus. *Eli Lilly* at 1406; MPEP 2163 (II)(A)(3)(a)(ii) at p. 2100-169, col. 1.

Thus, there is no fixed set of tests for whether a claimed genus is adequately described. Instead, the determination of compliance with the written description requirement is a fact-based one, and in cases subsequent to *Eli Lilly*, the Federal Circuit has limited the holding in *Eli Lilly* to its particular set of facts. *E.g.*, *Moba* at 1320²; *Amgen* at 1332³; *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002); *but see University of Rochester v. G.D. Searle & Co., Inc.*, Slip. Op. 03-1304 (Fed. Cir. Feb. 13, 2004).

1 "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." (citation omitted).

2 "Invoking § 112, *Lilly* required a precise definition of a DNA sequence in the patent specification. *In more recent cases, however, this court has distinguished Lilly.*" (emphasis added).

3 "Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend."

Claims 3, 12, 15, 18, 43, 44, 48, 56, 58, 60, 62, 63, 70, and 77 have been cancelled. Accordingly, the rejection is moot as applied to these claims.

Concerning the remaining claims, the specification clearly conveys that the inventors contemplated the claimed genus of substitution mutants. Applicants have amended independent claims 1, 2, and 47 to recite a *Pol I type DNA polymerase* comprising one or more specified modifications. As amended, the claims encompass a genus of modified Pol I type DNA polymerases whose structure is well known in the art.

As discussed in previous replies, the specification describes a broad genus of enzymes, as well as subspecies and specific examples, that could serve as the backbone for making the recited substitutions of the invention. These "backbone" sequences need not have been provided in the specification because they were known. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94 (holding that the description only needs to describe what is new or not conventional); MPEP 2163, p. 2100-165, col. 2 (Rev. 1, Feb. 2003).

In addition, the skill and knowledge in the art at the time of filing was substantial. Information regarding Pol I type DNA polymerases and their domain structure is available to a person skilled in the art, including the localization of certain activities to specific domains. For example, the 5'-3' exonuclease domain of *E. coli* polymerase I is at the N-terminal end of the polymerase, while the middle and C-terminal domains of this polymerase exhibit 3'-5' exonuclease and DNA polymerase activity, respectively. *See*, C. M. Joyce, *Curr. Opin. Str. Biol.* 1:123-129 (1991) (reference AR16). This domain structure is conserved in other Pol I-type polymerases, such as *The* DNA polymerase.

Further information regarding the domain structure of Pol I type DNA polymerases can be obtained from the functional characterization of deletion mutants of several other Pol I-type polymerases. For example, deletion of the first 235 and 288 amino acids from the N-terminal region of *Taq* polymerase eliminates 5'-3' exonuclease activity. Similarly, deletion of the first 250 amino acids of the *Tth* polymerase and the first 323 amino acids of *E. coli* polymerase I also eliminates 5'-3' exonuclease activity. Deletion of the first 514 and 520 amino acids from the N-terminal region of *E. coli* polymerase I eliminates both 5'-3' and 3'-5' exonuclease activity. Thus, the sequence and other information disclosed for DNA polymerases would indicate to a person skilled in the art that polymerase activity is localized to the C-terminal portion of the *Tne* DNA polymerase, while the 5'-3' and 3'-5' exonuclease activities are localized to the N-terminal and middle portions of this polymerase, respectively. Fragments containing the C-terminal region will typically retain polymerase activity, while fragments lacking the 5'-3' or 3'-5' exonuclease domains will not retain 5'-3' or 3'-5' exonuclease activity, respectively.

Additional information regarding the domain structure of Pol I type DNA polymerases can be obtained from mutational analyses that have been performed in the 3'-5' exonuclease domain of *E. coli* polymerase I. See Derbyshire *et al.*, *Science* 240:199-201 (1988) (reference AR8); and Derbyshire *et al.*, *EMBO J.* 10:17-24 (1991) (reference AS8). The mutations that resulted in loss of exonuclease activity, at residues 355, 424 and 501 were located in the regions of the 3'-5' exonuclease domain exhibiting a high degree of homology with *Tne* DNA polymerase and other members of the *E. coli* polymerase I family of polymerases. This information enables one skilled in the art to

envision numerous specific mutations that will reduce or eliminate 3'-5' exonuclease activity.

Further, the modifications recited in the independent claims are all in the O-helix region. As the specification states, "the O-helix region typically defines the nucleotide binding domain of DNA polymerases." Specification, p. 19, lines 7-8. Further,

The O-helix has been identified and defined for a number of polymerases and may be readily identified for other polymerases by one with skill in the art. Thus, given the defined O-helix region and the assays described in the present application, one with skill in the art can make one or a number of modifications which would result in increased fidelity of the polymerase.

Specification, p. 20, lines 10-14. The specification also provides the O-helix regions for a number of known polymerases on page 20, and the positions of the amino acids corresponding to the recited amino acids for a number of polymerases on page 21. Clearly, the specification conveys to one of ordinary skill in the art that the inventors contemplated the claimed genus. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph -new matter

Claims 1-9, 1-9, 11, 12, 14, 15, 17, 18, 20, 37-40, 43-48, and 50-82 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing new matter in the recitation beginning, "with the proviso that." Office Action, p. 7. Applicants respectfully traverse.

Applicants note that one or more of the provisos contained in the rejected claims are not described *in ipso verbis* in the present specification. However, such provisos need not be supported by specific language in the specification in order to be fully supported:

That what [patent applicants] claim as patentable to them is *less* than what they describe as their invention is not conclusive if their specification also reasonably describes that which they do claim.

In re Wertheim, 541 F.2d 257, 263 (C.C.P.A. 1976) (emphasis in original). Moreover, it has long been established law that excluding from a claim one or more species that are encompassed by a described genus does not violate the written description requirement under 35 U.S.C. § 112, first paragraph:

The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species there within, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute.

In re Johnson and Farnham, 558 F.2d 1008, 1019, 194 USPQ 195, 196 (C.C.P.A. 1977). Hence, since the present specification clearly describes the subject matter that *is* encompassed by the rejected claims, the proviso(s) excluding certain subject matter disclosed in the present specification does not violate the written description requirement under 35 U.S.C. § 112, first paragraph.

Nevertheless, to expedite prosecution, Applicants have amended independent claims 1, 2, and 47 to omit the provisos that the Examiner found objectionable. As amended, the claims recite particular amino acid substitutions that are listed in the specification, for example, at page 19, line 17 to page 20, line 9. Since the specification supports the recitation of each amino acid individually, the recited groups of amino acids are also supported by the specification.

Accordingly, claims 1, 2, and 47, and the claims dependent thereon, are adequately supported by the specification and do not contain new matter. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and request that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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